

## REMARKS

These remarks are in response to the Final Office Action mailed August 4, 2003.

Applicant thanks Examiner Maier for granting an interview on January 23, 2004, and for her helpful suggestions. Claims 171-197, 201, and 203-206 are pending and under examination. Claims 171, 178, 181, 188, 195, 201, 203, 204, 205, and 206 have been amended.

### Claim Rejections under 35 U.S.C. §103(a)

Claims 171-197, 201, and 203-206 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Hamann *et al.* (*J Immunol* (1995) 154(8): 4073-4080, henceforth “Hamann”) in view of Falk *et al.* (Pat. No. 5,827,834, henceforth “Falk”) for reasons set forth in the Office Action mailed November 19, 2002, and in the Final Office Action mailed August 4, 2003. (Hamann is Reference K and Falk is Reference A on PTO Form 892 dated May 8, 2000.)

Applicant respectfully traverses this rejection. Applicant submits that a *prima facie* case of obviousness has not been established by combining these references and therefore, the rejection under 35 U.S.C. § 103(a) is improper and should be withdrawn.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings to produce the claimed invention. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See, MPEP §§ 2142, 2143. In the present case, none of the criteria for a *prima facie* case of obviousness has been satisfied and therefore, the claim rejection under 35 U.S.C. §103(a) should be withdrawn.

### No suggestion or motivation to combine references to make the claimed methods

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q. 2d 1596 (Fed.

Cir. 1988); *In re Jones* 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992). See generally, MPEP §2143, especially §2143.01. Absent a suggestion, teaching, or motivation to combine references, such a combination is unacceptable “hindsight” that does not establish a *prima facie* case of obviousness. *In re Dembiczak* 175 F.3d 994, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999).

Contrary to the assertion that “the steps of the claimed methods are reasonably suggested by the prior art as applied” (Final Office Action (Final OA), page 2, lines 17-19), neither reference teaches or suggests combining Hamann and Falk to produce the claimed methods. As acknowledged in the Office Action mailed November 19, 2002, Falk “teaches that hyaluronic acid may be administered to patients” (page 4, lines 16-17) but “Hamann does not explicitly teach administering hyaluronic acid to a patient” (page 4, lines 14-15). Therefore, there is no teaching or suggestion in the references for the cited combination.

Applicant is unable to find motivation to combine Hamann and Falk. Hamann disclosed that *in vitro* HA-induced cell proliferation requires attachment of the cell surface to HA attached to a solid phase (page 4077 and Figure 5), such that the HA is not released into the culture medium. Further, the HA effects disclosed by Hamann were seen in cells cultured with recombinant IL-3 and IL-5 (page 4074, left column, lines 13-16 and right column, line 15-17). The effects of culturing cells in the presence of only solid phase HA without cytokine supplementation, are not disclosed. These *in vitro* results fail to provide motivation to one of ordinary skill in the art to administer HA *in vivo*.

**The references teach away from combination**

Further, it is improper to combine references where the references teach away from their combination. *In re Grasselli*, 218 USPQ 769 (Fed. Cir. 1983). Here, Hamann’s results teach away from combining Hamann’s disclosure of *in vitro* HA-induced effects on cell proliferation and differentiation, with Falk’s disclosure of *in vivo* administration of HA. Hamann discloses heterogeneous effects of immobilized HA on umbilical cord blood mononuclear cell (MNC) subpopulations: (1) HA enhanced proliferation and differentiation of a fractionated population of CD34+ progenitor cells; and (2) HA actually inhibited proliferation and differentiation of unfractionated cord blood MNC. (Hamann, page 4076, “Effect of HA on development of cord blood progenitor cells” and Figures 5 and 6). This *in vitro* result teaches away from using HA *in*

*vivo* to stimulate cell proliferation (*i.e.*, combining Hamann and Falk), as HA would be expected to encounter a variety of cell subpopulations *in vivo*, analogous to Hamann's study of unfractionated cord blood.

Because there is no teaching, suggestion, or motivation to combine the cited references to produce the claimed methods, either in the references themselves or in the knowledge available to one of skill in the art, this criterion for establishing a *prima facie* case of obviousness has not been satisfied, and the rejection should be withdrawn.

**No reasonable expectation of success**

The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 U.S.P.Q. 375 (Fed. Cir. 1986). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). As noted above, Hamann disclosed that HA-induced cell proliferation requires attachment of the cell surface to immobilized HA (page 4077 and Figure 5), the HA effects were only measured under conditions of cytokine supplementation (page 4074, left column, lines 13-16 and right column, line 15-17), and HA had heterogeneous effects on different umbilical cord blood MNC subpopulations. Hamann's disclosure of *in vitro* results obtained under defined reaction conditions, provides no reasonable expectation of success for *in vivo* administration of HA. Neither reference suggests there is any advantage to modifying or combining the steps of these references to produce the claimed methods.

**The combination of prior art references do not teach or suggest all claim limitations**

To establish *prima facie* obviousness of a claimed methods, all the claim limitations must be taught or suggested by the prior art. *In re Royka* 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). In the present case, the cited combination of Hamann in view of Falk does not teach all the claim limitations.

Applicant wishes to traverse the assertions in the Final Office Action that “[t]he invention need not be taught in the references” and “[u]nder §103, a reasonable suggestion of the claimed methods to one of ordinary skill in the art based on properly combined references, and a

reasonable expectation of success, are sufficient" (Final OA, page 2, lines 12-13), on the grounds that these statements appear to be contrary to established law regarding establishing a *prima facie* case of obviousness under 35 U.S.C. §103. See, MPEP §2132.03 and references cited therein.

Here, Hamann allegedly "teaches that hyaluronic acid as claimed has the necessary activity *in vitro*" and Falk allegedly "discloses that hyaluronic acid is suitable for administration to patients" (Final OA, page 3, lines 8-10). Hamann is "the reference relied upon for the teaching of the pharmaceutical activity underlying the claimed methods" (Final OA, page 3, lines 17-19) on grounds that Hamann allegedly "discloses that HA causes a concentration-related increase in proliferation of CD34+ eosinophil progenitor cells" (Final OA, page 2, line 20, to page 3, line 1). Applicant respectfully points out that Hamann does not disclose releasing cells from bone marrow and other tissue sites, nor increasing the number of stem cells in the blood, nor mobilizing cells.

In conclusion, the combination of Hamann, in light of Falk, does not teach the claim limitations of the present invention. Because the combination of prior art references does not teach or suggest all the claim limitations, no *prima facie* case of obviousness has been established and the rejection should be withdrawn.

#### Summary

In sum, no *prima facie* case of obviousness has been established. The cited references fail to teach, suggest, or provide motivation for combining or modifying the references to produce the methods of Claims 171-197, 201, and 203-206, and likewise fail to provide guidance as to how to combine or modify references to produce the claimed methods. In fact, the Hamann reference teaches away from the cited combination, making the combination improper. The cited combination fails to provide a reasonable expectation of success from combining or modifying the methods in the cited references. The cited references fail to teach or suggest all the claim limitations of Claims 171-197, 201, and 203-206. Thus, it cannot objectively be stated that the skilled artisan could combine or modify the cited references in such a way as to produce the claimed methods, let alone that the skilled artisan would be motivated to combine these references or that there would be a reasonable expectation of success. Because none of the

criteria for establishing a *prima facie* case of obviousness has been satisfied, the rejection under 35 U.S.C. §103(a) is improper and must be withdrawn.

### CONCLUSION

Claims 171-197, 201, and 203-206 are pending in the application. Claims 171-197, 201, and 203-206 were rejected in the Office Action mailed August 4, 2003. Claims 171, 178, 181, 188, 195, 201, 203, 204, 205, and 206 have been amended. Applicant requests entry of claim amendments and new claims, with the result that Claims 171-197, 201, and 203-206 are pending in the application. Applicant requests that claim rejections be reconsidered and withdrawn in light of the foregoing remarks, and that pending claims be found in condition for allowance.

If the Examiner believes that a telephone interview would expedite prosecution of this application, she is encouraged to telephone the undersigned Applicant's attorney.

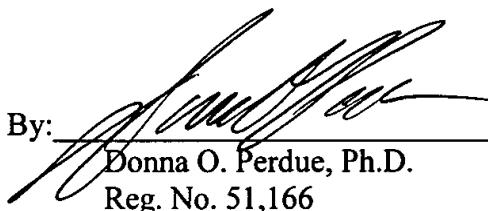
If the fee authorized is incorrect or if any other fees are due in connection with this submission, please charge any such fee or credit any overpayment to Deposit Account No. 50-2212.

Respectfully submitted,

PILLSBURY WINTHROP LLP

Date: Feb 4, 2004

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